REMARKS/ARGUMENTS

Reconsideration of this application and entry of this Amendment are requested. Claims 180-189 will be active in the application subsequent to entry of this Amendment. The issues raised in the outstanding Official Action will be addressed in the remarks that follow.

Discussion of Amended Claims

The claims have been amended as set out in the accompanying set of claims.[1] All are directed to methods of delivering/administering a beneficial substance associated with a resorbable silicon carrier material as in previous claim 177.

Claim 180

Basis for claim 180 may be found in the papers as originally filed. For example, please refer to claim 33, page 32 of the description (which describes subcutaneous in-vivo trials), plus the more general statements at page 9, line 20, page 16, line 27 and page 26, lines 27-28.

Claim 181

Page 3, lines 15-19.

Claim 182

Page 3, lines 15-19.

Claim 183

Page 3, line 16 and page 14, line 18.

Claim 184

Page 7, lines 20-22.

Claim 185

Page 5, line 18.

Claim 186

Page 7, lines 1-5.

Claim 187

Page 7, lines 7-9.

[1] Basis is with reference to the published PCT application.

Claim 188

Page 15, part (b) describes how the silicon samples were doped with phosphorus. The samples are then porosified.

Claim 189

Page 27, lines 24-25.

The outstanding Official Action includes rejections under 35 USC §112, first and second paragraphs. The examiner's previous objections have been taken into account when preparing the new set of claims presented above. Basis in the original description is explained in detail in the above summary. The claims have been drafted to provide for the requisite degree of clarity, thus the rejections under 35 USC §112, first and second paragraphs are not pertinent to the claims presented above.

Response to Prior Art-Based Rejections

The Official Action includes two prior art-based rejections and it would appear that the new claims presented above, directed to methods of administering a beneficial substance by subcutaneously implanting an implant of the type defined are most similar to previous claim 177. Accordingly, the only pertinent prior art rejection is one of alleged "obviousness" based upon the disclosures of published PCT application WO 97/06101 to Canham, the senior inventor and applicant in respect to the present application as well.

Novelty

WO 97/06101 (Canham) does not disclose a method of delivering a beneficial substance to a human or animal subject subcutaneously. By way of background, the subcutaneous layer (sometimes referred to as the subcutis) is the layer of tissue directly underlying the cutis (the two outer layers of skin) and is mainly composed of adipose tissue. Its physiological function includes insulation and storage of nutrients. It is known to administer injections subcutaneously.

In addition, Canham does not disclose a method of delivering a beneficial substance to a human or animal subject subcutaneously using resorbable mesoporous silicon.

Nonobviousness

The amended claims are also inventive over Canham.

Canham centers around the ability of silicon to form bonds with bone. The ability of silicon to form bonds with bone means the silicon is bioactive.

The precise nature of the silicon is important in determining whether or not a bond will form between the silicon and bone. It is likely that the silicon has to be in a form which gives it the ability to form nucleation sites for the formation of calcium phosphate which in turn forms hydroxyapatite (the inorganic phase of bone).

Put another way, Canham illustrates a form of bioactivity wherein calcification results. For example, Figure 3 illustrates the formation of apatite (region C) indicating the ability of the silicon to bond to bone. Hence Canham clearly illustrates that certain silicon samples are useful at skeletal sites. The subcutaneous layer is not a skeletal site.

The present invention is concerned with the delivery of beneficial substances, such as drugs, following implantation in the subcutaneous layer, in other words at soft tissue sites. If these subcutaneously implanted samples were to calcify in the proximity of soft tissue, then this would give rise to significant problems. Firstly, calcification in a soft tissue environment is undesirable from a toxicology standpoint. Further, in-vivo deposition of calcium phosphate coatings will impede silicon resorption and will inhibit drug delivery.

The present invention centers around the finding that mesoporous silicon can resorb following implantation in the subcutaneous layer. This would not have been obvious from the teaching of Canham

The (apparent) most relevant sections of Canham, at least so far as the Examiner is concerned, are possibly the final paragraph on page 12 and lines 20-24 of page 17. Applicants address these passages as follows:

Canham, page 12, final paragraph

A mesoporous porous silicon sample was immersed in Simulated Body Fluid (SBF). After one day the sample had been dissolved by the SBF. Such a result does not provide an indication of how such a sample would behave when implanted in the subcutaneous layer. In addition, the teaching of Canham in its entirety would suggest that, in all likelihood, calcification would also occur.

Canham, page 17, lines 20-24

This section in Canham presents the case that the experiments which have been carried out in Simulated Body Fluid do not necessarily provide a clear indication of the suitability of a particular form of porous silicon for resorbable material applications and that it may be necessary

to carry out in-vivo experiments to determine whether a particular desired physiological response is achieved.

In other words, this section acknowledges that the results in SBF are interesting, they do not necessarily provide a reliable model for particular sites in the body. In other words, a reasonable expectation is not provided by the Canham reference. There is no suggestion in Canham to use mesoporous silicon in the subcutaneous layer.

There are a broad range of physiological environments in the body which provide very different environments and therefore different challenges in developing a sample of silicon which will be suitable for use in a particular environment.

As will be apparent to any researcher working in the drug delivery field, huge resources in the pharmaceutical industry are needed in developing different forms of a drug for different administration routes. Simulated Body Fluid (SBF) is significantly different from the fluid found in the subcutaneous layer. The main fluid found in the subcutaneous layer is human plasma. Human plasma is a complex mixture of constituents which, unlike SBF, comprises hugely complex materials such as cells and proteins. It is difficult to predict how a material such as porous silicon will interact with these complex biological molecules. The skilled person on reading Canham might expect that that some calcification would occur and a bond would start to form between the cells and proteins in the human plasma and the porous silicon. This would seriously inhibit the efficacy of the implant.

On the basis of this argument alone, it is considered that the claims of the present invention are inventive over Canham. However, it is also worth considering a comparison of some of the experimental results in the present application over Canham.

Comparison of experimental results

Figures 2A-2D of the present application show scanning electron micrographs of a 30% mesoporous silicon subcutaneous implant explanted from a guinea pig at 0,1, 4 and 12 weeks after implant (see page 13, lines 5-7 and page 14, lines 17-22).

As set out in the present application on page 14, lines 17-22, Figures 2A-2D clearly show that there was considerable corrosion of the subcutaneous porous silicon.

Page 17 (first paragraph) of the present application goes on to describe how the 12 week tests were followed by a 26 week study which showed entirely consistent results. There was a

steady corrosion of porous silicon and the corrosion of the implants did not cause any significant harmful effects on the test subjects. There was no gross inflammatory response, no significant fibrotic scarring, and excreting the corroded silicon was not a problem.

These results illustrate how steady and continuous the rate of corrosion can be when porous silicon is implanted subcutaneously. In other words, it is suitable for the delivery of drugs over a significant period of time which is crucially important for subcutaneous delivery of drugs. This could not have been predicted from the teaching of Canham. The teaching in Canham at page 12 is that in SBF the porous silicon sample is dissolved in a single day.

In summary, there are a number of persuasive components of applicants' position: First of all, the teaching of Canham would mean the skilled person would have no insight into the suitability of using porous silicon for subcutaneous implantations. There is no suggestion by Canham to use porous silicon in such a mode of delivery. From a fair reading of Canham, the skilled person could also have reasonably expected that calcification of the porous silicon would have occurred in-situ which would have meant subcutaneous delivery was not realistically possible. Finally, the immersion of porous silicon in SBF in Canham resulted in a rate of corrosion which would not motivate the skilled person to consider that mesoporous silicon would be suitable for subcutaneous implantation.

For the above reasons it is respectfully submitted that claims 180-189 as above presented are fairly based in the original disclosure, i.e. there is no added subject matter in these claims, and the claims are patentable over the Canham reference. Reconsideration, entry of this Amendment and allowance are solicited.

For the above reasons it is respectfully submitted that claims 180-189, all of the claims in the application, define inventive subject matter. Reconsideration and allowance are solicited.

Respectfully submitted,

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